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Co-formability, solubility enhancement and stability of olanzapine co-amorphous systems produced with different co-formers

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ABSTRACT

Introduction: Strategies to address the problem of poorly water-soluble drugs encompass the conversion of a crystalline drug into an amorphous form to promote its apparent solubility and dissolution. Co-amorphous systems (CAMs) incorporate low molecular mass molecules (co-formers), which are mixed with the drug to form one single phase [1,2]. The aim of this study is to understand the capability of different co-formers (amino, carboxylic and sulphonic acids), in the production of CAMs with olanzapine by ball milling, solvent evaporation and quench cooling.

Materials and methods: Mixtures (2 g) of olanzapine (OLZ) and each co-former [L-aspartate (ASP); L-tryptophan (TRY); L-arginine (ARG); L-proline (PRO); citric acid (CIT); tartaric acid (TAR); oxalic acid (OXA); saccharine (SAC); potassium acessulfame (ACE); cyclamic acid (CYC)] in 1:1 molar ratios were submitted to ball milling (BM), solvent evaporation (SE) and quench cooling (QC). CAMs were evaluated for the OLZ solubility increase, co-formability and storage stability over time, by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and Fourier-transform infra-red spectroscopy (FTIR).

Results: The BM technique presented the most promising results followed by QC and SE (Table 1), since more CAMs were produced. All the sulphonic acids (SAC, CYC and ACE) formed CAMs regardless of the technique used, presenting complete amorphization probably due to their higher ability to produce intermolecular interactions, like hydrogen-bonding, thus increasing the stability of CAMs (more than 8 weeks at 25 °C/11 and 53% RH). Conversely, amino acids were the least efficient in producing CAMs. Crystalline OLZ presented low solubility (40.1 mg/L) in water and a general increase in the solubility of the CAMs was observed. Carboxylic acids (TAR, CIT, OXA) achieved the biggest increase (up to 269 times, BM with TART) followed by sulphonic acids (up to 199 times, SE with SAC), unveiling the possibility of improved dissolution profiles and bioavailability.

Discussion and conclusions: The study has shown the possibility of converting a crystalline drug into an amorphous entity, particularly when in presence of co-formers which stabilise the amorphous structures formed. In fact, with sulphonic acids, both SE and BM, achieved complete amorphization and successfully stabilised the CAMs obtained. Due to the noteworthy increase in solubility, resulting from co-amorphization, this technique is considered to be adequate to process active compounds with poor water solubility, such as OLZ.

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Table 1. Comparison of the of co-amorphization ability using different techniques and co-formers.

Mixtures	QC	SE	BM
OLZ:PRO	Yes[a]	No	No
OLZ:ARG	No	No	No
OLZ:TRY	No	No	Yes[a]
OLZ:SER	No	No	No
OLZ:ASP	No	No	Yes[a]
OLZ:CIT	Yes[a]	No	Yes[b]
OLZ:TAR	Yes[a]	No	Yes[b]
OLZ:OXA	Yes[a]	No	No
OLZ:SAC	Yes[b]	Yes[b]	Yes[b]
OLZ:CYC	No	Yes[b]	Yes[b]
OLZ:ACE	Yes[b]	Yes[b]	Yes[b]

[a]Incomplete amorphization; [b]complete amorphization.

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Comparison of the amorphization ability of two polymorphic forms of olanzapine

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ABSTRACT

Introduction: The production of amorphous and co-amorphous (CAM) materials has been used as a procedure to overcome the poor water solubility shown by most of the drugs currently under development [1]. Ball milling has been considered to convert the crystalline state of a substance into its amorphous counterpart [2,3]. At present, the impact of the initial polymorphic form of a drug substance on its final amorphous state upon milling, has not been clearly studied. This work aims to compare the co-amorphization efficiency of two different polymorphic forms of olanzapine (OLZ; a BCS class II drug) using saccharin (SAC) as a co-former.

Materials and methods: OLZ (forms I and II) were the starting polymorphic forms to be milled with SAC (2:1 molar ratio). OLZ form I was used as received while OLZ form II was obtained from crystallisation of OLZ in dichloromethane. Ball milling was performed using 2.5 g of 3.0 mm Ø balls, for 2 h. The conversion of the crystalline states into the amorphous counterpart was monitored by calorimetry (DSC) and diffractometry (XRPD).

Results: The thermograms and the diffractograms obtained (Figure 1) have shown a clear difference between the final products of the two polymorphic forms of OLZ. XRPD peaks were less intense for OLZ form II and most representative of SAC, indicating that OLZ was indeed mostly converted into the amorphous state. On the other hand, when OLZ form I was the starting material, a richer diffractogram resulted, suggesting that a crystalline fraction of OLZ remained in the particles' network of the final product, a feature also confirmed by DSC.

Discussion and conclusions: Since OLZ form II has a higher thermodynamic energy than form I, it is not surprising that the former exhibits better amorphization ability. Thus, it is expected that either an increase on milling time, or milling speed, would enhance the co-amorphization of OLZ form I with SAC.

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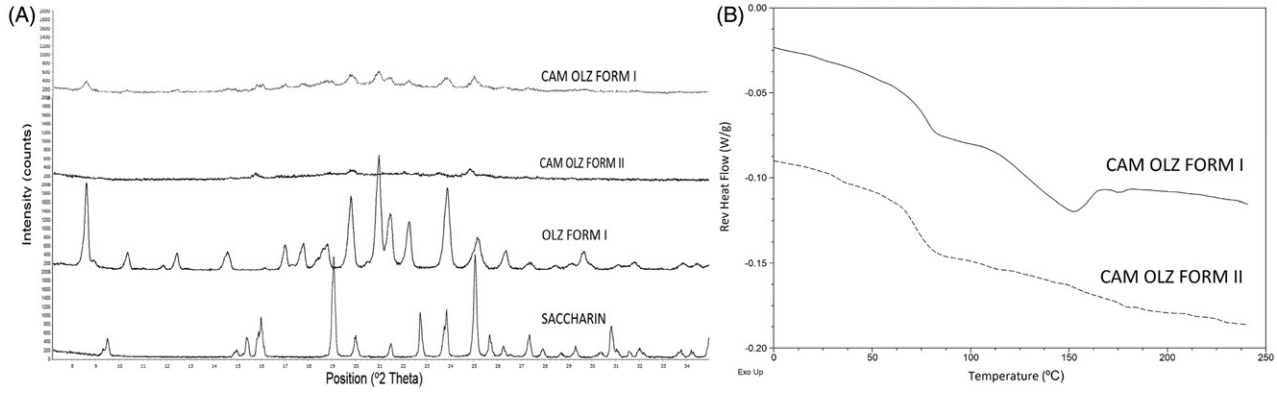

Figure 1. X-ray diffractograms (A) and DSC thermograms (B) of the different molecular entities..